## APPENDIX A

1. An LHRH antagonist, comprising a peptide having a sidechain modified by a dipolar moiety forming a modified peptide, such that the modified peptide has LHRH antagonist activity.

2. The LHRH antagonist of claim 1, wherein the dipolar moiety is selected from the group consisting of ylids, tertiary amine oxides, nitrile oxides, pyridine-N-oxides, and pyridinium zwitterions.

3. The LHRH antagonist of claim 1, wherein the dipolar moiety is an ylid.

4. The LHRH antagonist of claim 1, wherein the dipolar moiety is a pyridine-N-oxide.

5. The LHRH antagonist of claim 1, wherein the dipolar moiety is a pyridinium zwitterion.

6. The LHRH antagonist of claim 1, wherein the peptide comprises about 8 to about 12 residues.

7. The LHRH antagonist of claim 1, wherein the peptide comprises 10 residues.

8. The LHRH antagonist of claim 1, wherein the dipolar moiety modifies residue 6.

9. The LHRH antagonist of claim 1, wherein the LHRH antagonist is a peptide mimetic.

10. A peptide comprising a structure:

A-B-C-D-E-F-G-H-I-J

wherein

A is pyro-Glu, Ac-D-Nal , Ac-D-Qal, Ac-Sar, or Ac-D-Pal

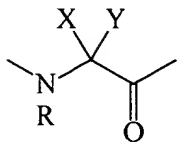
B is His or 4-Cl-D-Phe

C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp

D is Ser

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is



wherein

R and X are, independently, H or alkyl; and

Y comprises a dipolar moiety;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg

I is Pro; and

J is Gly-$NH_2$ or D-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

11. The peptide of claim 10, wherein Y is selected from the group consisting of ylids, tertiary amine oxides, nitrile oxides, pyridine-N-oxides, and pyridinium zwitterions.

12. The peptide of claim 10, wherein Y is an ylid.

13. The peptide of claim 10, wherein Y is a pyridine-N-oxide.

14. The peptide of claim 10, wherein the dipolar moiety is a pyridinium zwitterion.

15. A peptide comprising a structure:
Ac-D-Nal-4-Cl-Phe-D-Pal-Ser-Tyr-D-Pal(N-O)-Leu-Lys(iPr)-Pro-D-Ala-$NH_2$.

16. A peptide comprising a structure
Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-Tyr-D-Pal($CH_2COO^-$)-Leu-Lys(iPr)-Pro-Ala-$NH_2$;
or a pharmaceutically acceptable salt thereof.

17. An LHRH antagonist, comprising a peptide having a sidechain modified by a cationic moiety selected from the group consisting of cationic pyridinium moieties and

sulfonium moieties, with the proviso that the cationic moiety is not N-methyl pyridinium, forming a modified peptide, such that the modified peptide has LHRH antagonist activity.

18. The LHRH antagonist of claim 17, wherein the cationic moiety is a cationic pyridinium moiety.

19. The LHRH antagonist of claim 17, wherein the cationic moiety is a sulfonium moiety.

20. The LHRH antagonist of claim 17, wherein the peptide comprises about 8 to about 12 residues.

21. The LHRH antagonist of claim 17, wherein the peptide comprises 10 residues.

22. The LHRH antagonist of claim 17, wherein the cationic moiety modifies at least one of residue 6 and residue 8.

23. The LHRH antagonist of claim 17, wherein the LHRH antagonist is a peptide mimetic.

24. A peptide comprising a structure:

A-B-C-D-E-F-G-H-I-J

wherein

A is pyro-Glu, Ac-D-Nal , Ac-D-Qal, Ac-Sar, or Ac-D-Pal

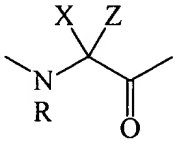
B is His or 4-Cl-D-Phe

C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp

D is Ser

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is D-Arg, D-Lys(iPr), D-Pal(iPr), D-Cit or Q, wherein Q has a structure




wherein

R and X are, independently, H or alkyl; and

Z comprises a cationic moiety selected from the group consisting of cationic pyridinium moieties and sulfonium moieties, with the proviso that the cationic moiety is not N-methyl pyridinium;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, Arg or Q;

I is Pro; and

J is Gly-$NH_2$ or D-Ala-$NH_2$;

with the proviso that at least one of F and H is Q;

or a pharmaceutically acceptable salt thereof.

25. The peptide of claim 24, wherein F is Q and Z is a cationic pyridinium moiety.

26. The peptide of claim 25, wherein Z is an N-benzyl pyridinium moiety.

27. A peptide comprising a structure

Ac-Sar-4-Cl-D-Phe-D-Nal-Ser-Tyr-D-Pal(Bzl)-Leu-Lys(iPr)-Pro-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

28. The peptide of claim 24, wherein F is Q and Z is a sulfonium moiety.

29. A peptide comprising a structure:

Ac-D-Nal-4-Cl-D-Phe-D-Trp-Ser-Tyr-D-Met($S^+Me$)-Leu-Arg-Pro-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

30. The peptide of claim 24, wherein H is Q and Z is a sulfonium moiety.

31. A peptide comprising a structure:

Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-Tyr-D-Arg-Leu-Met($S^+Me$)-Pro-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

32. An LHRH antagonist, comprising a peptide having a sidechain modified by a receptor-modifying moiety forming a modified peptide, such that the modified peptide has LHRH antagonist activity.

33. The LHRH antagonist of claim 32, wherein the receptor-modifying moiety is selected from the group consisting of ylids, sulfonium moieties, α-halocarbonyls, sulfates, sulfonates alkyl halides, and benzyl halides.

34. The LHRH antagonist of claim 32, wherein the peptide comprises about 8 to 12 residues.

35. The LHRH antagonist of claim 32, wherein the peptide comprises 10 residues.

36. The LHRH antagonist of claim 32, wherein the receptor-modifying moiety modifies residue 6.

37. The LHRH antagonist of claim 32, wherein the LHRH antagonist is a peptide mimetic.

38. A peptide comprising a structure:

A-B-C-D-E-F-G-H-I-J

wherein

A is p-Glu, Ac-D-Nal , Ac-D-Qal, Ac-Sar, or Ac-D-Pal

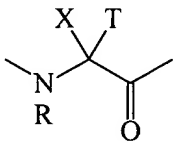
B is His or 4-Cl-D-Phe

C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp

D is Ser

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is




wherein

R and X are, independently, H or alkyl; and

T comprises a receptor-modifying moiety;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg

I is Pro; and

J is Gly-$NH_2$ or D-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

39. The peptide of claim 38, wherein T is selected from the group consisting of ylids, sulfonium moieties, α-halocarbonyls, sulfates, sulfonates, alkyl halides and benzyl halides.

40. The peptide of claim 39, wherein T is an α-halocarbonyl.

41. An LHRH antagonist, comprising a peptide having a sidechain modified by a hydrophilic N-acyl moiety forming a modified peptide, such that the modified peptide has LHRH antagonist activity.

42. The LHRH antagonist of claim 41, wherein the hydrophilic N-acyl moiety modifies position 6.

43. The LHRH antagonist of claim 41, wherein a residue comprises a hydrophilic acyl moiety selected from the group consisting of D-Lys(Imdac), D-Lys(Ppic) and D-Lys(Dodac).

44. The LHRH antagonist of claim 41, wherein the hydrophilic N-acyl moiety has a log P between -1 and +2.

45. A peptide comprising a structure:

A-B-C-D-E-F-G-H-I-J

wherein

A is pyro-Glu, Ac-D-Nal , Ac-D-Qal, Ac-Sar, or Ac-D-Pal

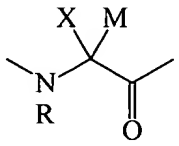
B is His or 4-Cl-D-Phe

C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp

D is Ser

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is



wherein

R and X are, independently, H or alkyl; and

M comprises an N-acyl hydrophilic moiety;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg

I is Pro; and

J is Gly-$NH_2$ or D-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

46. The peptide of claim 44, wherein F is selected from the group consisting of D-Lys(Imdac), D-Lys(Ppic) and D-Lys(Dodac).

47. A peptide comprising a structure:

Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-Tyr-D-Lys(Imdac)-Leu-Lys(iPr)-Pro-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

61. An LHRH antagonist comprising a peptide compound, wherein a residue of the peptide compound corresponding to the amino acid at position 6 of natural mammalian LHRH comprises a small polar moiety, said small polar moiety having a log P between -1 and +2, wherein the peptide compound has LHRH antagonist activity, inhibits ovulation in at least 50% of treated rats in a standard rat antiovulatory assay at a dose of 5 μg/rat, and has an $ED_{50}$ for histamine release of at least 3 μg/ml, or a pharmaceutically acceptable salt thereof.

62. The LHRH antagonist of claim 61, which inhibits ovulation in at least 50% of treated rats in a standard rat antiovulatory assay at a dose of 2 μg/rat.

63. The LHRH antagonist of claim 61, which inhibits ovulation in at least 50% of treated rats in a standard rat antiovulatory assay at a dose of 1 μg/rat.

64. The LHRH antagonist of claim 61, which has an $ED_{50}$ for histamine release of at least 5 μg/ml.

65. The LHRH antagonist of claim 61, which has an $ED_{50}$ for histamine release of at least 10 μg/ml.

66. The LHRH antagonist of claim 61, which is about 8 to about 12 residues in length.

67. The LHRH antagonist of claim 61, which is 9 to 11 residues in length.

68. The LHRH antagonist of claim 61, which is 10 residues in length.

69. The LHRH antagonist of claim 61, wherein the residue corresponding to the amino acid at position 6 of natural mammalian LHRH is selected from the group consisting of D-asparagine, D-threonine and D-glutamine.

70. The LHRH antagonist of claim 61, wherein the residue corresponding to the amino acid at position 6 of natural mammalian LHRH is D-asparagine.

71. A peptide compound comprising a structure:

A-B-C-D-E-F-G-H-I-J

wherein

A is pyro-Glu, Ac-D-Nal , Ac-D-Qal, Ac-Sar, or Ac-D-Pal;

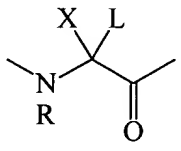
B is His or 4-Cl-D-Phe;

C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp;

D is Ser;

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is




wherein

R and X are, independently, H or alkyl; and

L comprises a small polar moiety, said small polar moiety having a log P between -1 and +2;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg;

I is Pro; and

J is Gly-$NH_2$ or D-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

72. The peptide of claim 71, wherein F is selected from the group consisting of D-Asn, D-Gln, and D-Thr.

73. A peptide compound comprising a structure:

A-B-C-D-E-F-G-H-I-J

wherein

A is pyro-Glu, Ac-D-Nal , Ac-D-Qal, Ac-Sar, or Ac-D-Pal;

B is His or 4-Cl-D-Phe;

C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-O), or D-Trp;

D is Ser;

E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile;

F is D-Asn;

G is Leu or Trp;

H is Lys(iPr), Gln, Met, or Arg;

I is Pro; and

J is Gly-$NH_2$ or D-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

74. A peptide compound comprising a structure:

Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-N-Me-Tyr-D-Asn-Leu-Lys(iPr)-Pro-D-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

75. A peptide compound comprising a structure:

Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-Tyr-D-Asn-Leu-Lys(iPr)-Pro-D-Ala-$NH_2$;

or a pharmaceutically acceptable salt thereof.

76. A pharmaceutical composition comprising the peptide compound of claim 61, and a pharmaceutically acceptable carrier.

77. A packaged formulation for treating a subject for a disorder associated with LHRH activity, comprising the peptide compound of claim 61 packaged with instructions for using the peptide compound for treating a subject having a disorder associated with LHRH activity.

78. A method of inhibiting LHRH activity associated with a cell, comprising contacting a cell with the peptide compound of claim 61, such that LHRH activity associated with the cell inhibited.

79. The method of claim 78, wherein the cell is within a subject and the peptide compound is administered to the subject.

80. A method of inhibiting growth of a hormone-dependent tumor in a subject, comprising administering to a subject an effective amount of the peptide compound of claim 61, such that growth of the hormone-dependent tumor in the subject is inhibited.

81. A method of inhibiting ovulation in a subject, comprising administering to a subject an effective amount of the peptide compound of claim 61, such that ovulation in the subject is inhibited.